

## **DETAILED ACTION**

### ***Continued Examination Under 37 CFR 1.114***

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 12/16/2010 has been entered.

#### Status of Claims:

Claims 17, 23, & 24 have been amended.

Claims 17-28 are currently under prosecution.

### ***Claim Rejections - 35 USC § 103***

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

The factual inquiries set forth in *Graham v. John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

**Claims 17-28 are rejected under 35 U.S.C. 103(a) as being unpatentable over Blankenstein US 6,432,630 in view of Mehta et al. US 6,632,655 in further view of Ishiguro et al. JP 2003-050245 (already of record).**

**Regarding claim 17, Blankenstein teaches** a chemical analytic apparatus (microflow system 1, figure 1, column 12 line 62 – column 13 line 12) which performs various kinds of processing for analyzing fluid chemically (column 1 lines 20-30), including:

in a condition where magnetic ultrafine particles (*magnetically stained particles 12 in sample 9, figure 1*) are mixed and contained inside a fluid (column 3 line 65 – column 4 line 10; column 12 lines 50-60, figure 1),

a conveyance means (*external magnet 8 proximate to flow channel 5 applies magnetic field to move magnetically stained particles to outlet 6; figure 1 column 12 lines 60-65*), wherein the fluid, to which said magnetic ultrafine particles were mixed is conveyed in another liquid (*buffers 10 & 11 enter flow channel, column 13 lines 1-5; furthermore, the magnet drives magnetic fluid to chamber 37 where it may contain washing fluid or reagents for reactions or analysis; column 17 lines 9-13*), for processing of chemical analysis, due to attraction by (*field generating means with a magnet 8, column 13 lines 1-5*) said magnetic ultrafine particles to the magnetic field of the conveyance means (*attracted to magnet, figure 6*); and

a processing means (*includes Blankenstein's step of selectively magnetically staining cells in a fluid containing target (cancer) cells and other cells, guiding a flow of the fluid containing the cancer cells through a flow channel in such a way that one cancer cell at the time passes a cross-section of the flow channel, positioning the flow channel in a magnetic field that is substantially perpendicular to a longitudinal axis of the flow channel so that magnetically stained cancer cells residing in the flow channel are deflected in the direction of the magnetic field, column 3 line 65 - column 4 line 10*) by which operations for processing of chemical analysis are performed one by one in the process in which the fluid to which said magnetic ultrafine particles were mixed is conveyed by said conveyance means (column 12 line 62 – column 13 line 12, figure 1), wherein

plural kinds of the fluid (*there is fluid containing target cells, fluid containing other cells, and suggested two buffers 10 & 11*) to which said magnetic ultrafine particles are mixed and of only the fluids are provided,

and said processing means is covered by thin plates (*Si wafer where flow channel 5 is etched onto column 13 lines 40-50 & figure 2*) at least on four side faces and a bottom face (*at least the bottom and side faces are the Si plate, See figure 2*) so as to be filled with another liquid,

Blankenstein further teaches a chemical reactive operation itself or part of the operation is performed by uniting the optional fluid in another compartment (*collection chamber 37 may contain a liquid or reagent fluid for further chemical reactions or analysis, column 17 lines 9-13*) with the another fluid out of said plural kinds arranged in the other small compartments. (*See figure 1, 6-7, column 1 lines 20-30, column 3 line 65 – column 4 line 10, column 12 lines 50-65, column 13 lines 1-15 & 40-50, column 16 lines 35-45*).

Blankenstein does not explicitly teach that the fluid is in the form of droplets. However, the term “droplet” does not add weight to the apparatus claim since “Expressions relating the apparatus to contents thereof during an intended operation are of no significance in determining patentability of the apparatus claim.” Ex parte Thibault, 164 USPQ 666, 667 (Bd. App. 1969). Furthermore, “[i]nclusion of material or article worked upon by a structure being claimed does not impart patentability to the claims.” See *In re Young*, 75 F.2d 996, 25 USPQ 69 (CCPA 1935) (as restated in *In re Otto*, 312 F.2d 937, 136 USPQ 458, 459 (CCPA 1963)) (see MPEP § 2115).

Blankenstein does not teach said processing means is separated by bulkheads into plural small compartments communicating with each other includes small compartments separated by plural bulkheads, and said plural kinds of the droplets to which said magnetic ultrafine particles were mixed and of only the droplets are arranged in said small compartments, and an optional droplet to which said magnetic ultrafine particles are mixed and which is arranged in an optional small compartment is conveyed by said conveyance means in the another liquid filling in the processing means while

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maintaining a single optional droplet in the another liquid, by passing through each bulkhead separating one small compartment from another.

However, Mehta teaches in (*column 16 line 55 - column 17 line 5*), an array of flowable or fixed particles sets used in microfluidic systems where in a region of channel 210, several particle retention regions 220-250 (*the bulkheads are considered as the pillars that separate each retention region*). Particles sets 260-290, which can comprise magnetic beads (*column 3 line 4*) movable by a proximate magnet control applying a magnetic field (*column 11 lines 1-5*) which are retained in the retention region, but communicated to neighboring regions by the narrow portion of channel 210 (*See figure 2A*) for localizing the particles that have adhered to target cells or analytes and separating them from the fluid, thus providing methods for sequencing nucleic acids (*column 3 lines 3-35*).

Therefore, it would have been obvious to one of ordinary skill in the art at the time of the invention to add protrusion elements such as the bulkheads taught by Mehta in the fluidic system of Blankenstein to retain the magnetic beads or particles and separate them from the fluid, which can provide methods for sequencing nucleic acids (*column 3 lines 3-35*).

It is noted that the optional language in the claim (i.e. "optional droplet" and "optional compartment") indicates that the feature does not have to be present in order to practice the claimed invention. Further, Blankenstein recites up to three liquids and Mehta discloses multiple compartments separated by bulkheads.

Blankenstein does not teach the magnet or conveyance means moving in a direction while applying a magnetic field, rather the magnet (8) is stationary as it's applying the magnetic field.

In the analogous art of particle separation in fluids, Ishiguro teaches a magnet that translate (*magnet 13, figure 3, [0011]*) rightward in the fluidic apparatus that moves magnetic fluid that was introduced into microchannels (3) towards capacity portions (1, 2), for the benefit of driving magnetic particles across a distance within a channel.

It would have been obvious to one of ordinary skill in the art to use a moving magnet of Ishiguro in the apparatus of Blankenstein to drive magnetic particles across a distance within a channel.

**Regarding claim 18, Blankenstein teaches** a fluid out of said plural kinds to which said magnetic ultrafine particles are mixed and which is conveyed to said other small compartments (*the chamber of outlet 6 is where the magnetically stained particles are transferred, figure 1*) where fluid and said magnetic ultrafine particles are mixed and separated (*separation occurs after magnet 8 toward sort outlet 6, figure 1*).

Blankenstein does not teach by said conveyance means by passing through each bulkhead separating one small compartment from another to a droplet that includes said magnetic ultrafine particles and the droplet that does not include said magnetic ultrafine particles by using physical and chemical characteristics such as wettability and surface tension of said optional droplet.

However, Mehta teaches in column 16 line 55 - column 17 line 5, an array of flowable or fixed particles sets used in microfluidic systems where in a region of channel 210, several particle retention regions 220-250 (*the bulkheads are considered as the pillars that separate each retention region*). Particles sets 260-290, which can comprise magnetic beads (*column 3 line 4*) movable by a proximate magnet control applying a magnetic field (*column 11 lines 1-5*) which are retained in the retention region, but communicated to neighboring regions by the narrow portion of channel 210, which fluid without the magnet particles flow through, (*See figure 2A*) for localizing the particles that have adhered to target cells or analytes and separating them from the fluid, thus providing methods for sequencing nucleic acids (*column 3 lines 3-35*).

Therefore, it would have been obvious to one of ordinary skill in the art at the time of the invention to add protrusion elements such as the bulkheads taught by Mehta in the fluidic system of Blankenstein to retain the magnetic beads or particles and separate them from the fluid, which can provide methods for sequencing nucleic acids (*column 3 lines 3-35*).

It is noted that the optional language in the claim (i.e. "optional droplet" and "optional compartment") indicates that the feature does not have to be present in order

to practice the claimed invention. Further, Blankenstein recites up to three liquids and Mehta discloses multiple compartments separated by bulkheads.

**Regarding claim 19, Blankenstein teaches** controlling the magnetic field which is externally applied to the droplet to which said magnetic ultrafine particles are mixed, said magnetic ultrafine particles are dispersed and cohered in the inside of the fluid, and also the operations for processing of chemical analysis of the droplet to which said magnetic ultrafine particles are mixed are performed. (*Column 3 line 65 – column 4 line 10 & column 5 line 60-65, column 6 line 20-35, & column 9 lines 10-40*).

**Regarding claim 20, Blankenstein** does not teach the physical and chemical reaction control by light, heat or pH is used.

However, Mehta teaches in (*column 5 lines 10-15*) teaches a control system that directs a plurality of mixings of the first reactant and the array wherein a reaction condition selected from temperature, pH, and time is systematically varied in separate mixings reactions. Other optional elements include a temperature control element for controlling temperature of reaction of the first and second element, a source of acid, a source of base and a source of reactants, reagents, array members, or the like (*column 5 lines 15-20*).

Therefore it would have been obvious to control the physical and chemical reaction conditions by heat, light, or pH, since the energy provided by these means are known to control the conditions of the reactions (*column 5 lines 15-20*).

**Regarding claim 21, Blankenstein** in the condition where a specimen for performing chemical reactive operation adhered (*magnetically stained particles, column 3 line 67 column 4 line 9*) to surfaces of said magnetic ultrafine particles, said magnetic ultrafine particles are used as a carrier to perform the chemical reactive operation to said specimen (*column 13 lines 1-15*).

**Regarding claims 22, Blankenstein does not teach** combining a plurality of said small compartments which are separated by plural bulkheads and which become said processing means, at least a series of chemical reactive operation by reaction, separation and dilution to a specimen that adhered to surfaces of said magnetic ultrafine particles is performed.

However, Mehta teaches in (*column 16 line 55 - column 17 line 5*), an array of flowable or fixed particles sets used in microfluidic systems where in a region of channel 210, several particle retention regions 220-250 (the bulkheads are considered as the pillars that separate each retention region). Particles sets 260-290, which can comprise magnetic beads (*column 3 line 4*) movable by a proximate magnet control applying a magnetic field (*column 11 lines 1-5*) which are retained in the retention region, but communicated to neighboring regions by the narrow portion of channel 210, which fluid without the magnet particles flow through, (*See figure 2A*) for localizing the particles that have adhered to target cells or analytes and separating them from the fluid, thus providing methods for sequencing nucleic acids (*column 3 lines 3-35*).

Therefore, it would have been obvious to one of ordinary skill in the art at the time of the invention to add protrusion elements such as the bulkheads taught by Mehta in the fluidic system of Blankenstein to retain the magnetic beads or particles and separate them from the fluid, which can provide methods for sequencing nucleic acids (*column 3 lines 3-35*).

**Regarding claim 23, Blankenstein teaches** a chemical analytic apparatus (*microflow system 1, figure 1, column 12 line 62 – column 13 line 12*) which performs various kinds of processing for analyzing very small droplets chemically (*column 1 lines 20-30*), including:

in a condition where magnetic ultrafine particles (*magnetically stained particles 12 in sample 9, figure 1*) are mixed and contained inside a fluid (*column 3 line 65 – column 4 line 10; column 12 lines 50-60, figure 1*),

a conveyance step (*external magnet 8 proximate to flow channel 5 applies magnetic field to move magnetically stained particles to outlet 6; figure 1 column 12 lines 60-65*), wherein the fluid, to which said magnetic ultrafine particles were mixed is conveyed in another liquid (*buffers 10 & 11 enter flow channel, column 13 lines 1-5; furthermore, the magnet drives magnetic fluid to chamber 37 where it may contain washing fluid or reagents for reactions or analysis; column 17 lines 9-13*), for processing of chemical analysis, due to attraction by (*field generating means with a magnet 8,*

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*column 13 lines 1-5) said magnetic ultrafine particles to the magnetic field of the conveyance means (attracted to magnet, figure 6); and*

*a processing step (includes Blankenstein's step of selectively magnetically staining cells in a fluid containing target (cancer) cells and other cells, guiding a flow of the fluid containing the cancer cells through a flow channel in such a way that one cancer cell at the time passes a cross-section of the flow channel, positioning the flow channel in a magnetic field that is substantially perpendicular to a longitudinal axis of the flow channel so that magnetically stained cancer cells residing in the flow channel are deflected in the direction of the magnetic field, column 3 line 65 - column 4 line 10)* by which operations for processing of chemical analysis are performed one by one in the process in which the droplet to which said magnetic ultrafine particles were mixed is conveyed by said conveyance step (*column 12 line 62 – column 13 line 12, figure 1*), wherein

*plural kinds of the fluid (there is fluid containing target cells, fluid containing other cells, and suggested two buffers 10 & 11) to which said magnetic ultrafine particles are mixed and of only the droplets are provided,*

*and said processing means is covered by thin plates (Si wafer where flow channel 5 is etched onto column 13 lines 40-50 & figure 2) at least on four side faces and a bottom face (at least the bottom and side faces are the Si plate, See figure 2) so as to be filled with another liquid,*

Blankenstein further teaches a chemical reactive operation itself or part of the operation is performed by uniting the optional droplet in another compartment (*collection chamber 37 may contain a liquid or reagent fluid, inherently droplet, for further chemical reactions or analysis, column 17 lines 9-13*) with the another droplet out of said plural kinds arranged in the other small compartments. (*See figure 1, 6-7, column 1 lines 20-30, column 3 line 65 – column 4 line 10, column 12 lines 50-65, column 13 lines 1-15 & 40-50, column 16 lines 35-45*).

Blankenstein does not explicitly teach that the fluid is in the form of droplets. However, the term “droplet” does not add weight to the apparatus claim since “Expressions relating the apparatus to contents thereof during an intended operation



are of no significance in determining patentability of the apparatus claim.” Ex parte Thibault, 164 USPQ 666, 667 (Bd. App. 1969). Furthermore, “[i]nclusion of material or article worked upon by a structure being claimed does not impart patentability to the claims.” See *In re Young*, 75 F.2d 996, 25 USPQ 69 (CCPA 1935) (as restated in *In re Otto*, 312 F.2d 937, 136 USPQ 458, 459 (CCPA 1963)) (see MPEP § 2115).

Blankenstein does not teach said processing means is separated by bulkheads into plural small compartments communicating with each other includes small compartments separated by plural bulkheads, and said plural kinds of the droplets to which said magnetic ultrafine particles were mixed and of only the droplets are arranged in said small compartments, and an optional droplet to which said magnetic ultrafine particles are mixed and which is arranged in an optional small compartment is conveyed by said conveyance means in the another liquid filling in the processing means while maintaining a single optional droplet in the another liquid, by passing through each bulkhead separating one small compartment from another.

However, Mehta teaches in (*column 16 line 55 - column 17 line 5*), an array of flowable or fixed particles sets used in microfluidic systems where in a region of channel 210, several particle retention regions 220-250 (the bulkheads are considered as the pillars that separate each retention region). Particles sets 260-290, which can comprise magnetic beads (*column 3 line 4*) movable by a proximate magnet control applying a magnetic field (*column 11 lines 1-5*) which are retained in the retention region, but communicated to neighboring regions by the narrow portion of channel 210 (See figure 2A) for localizing the particles that have adhered to target cells or analytes and separating them from the fluid, thus providing methods for sequencing nucleic acids (*column 3 lines 3-35*).

Therefore, it would have been obvious to one of ordinary skill in the art at the time of the invention to add protrusion elements such as the bulkheads taught by Mehta in the fluidic system of Blankenstein to retain the magnetic beads or particles and separate them from the fluid, which can provide methods for sequencing nucleic acids (*column 3 lines 3-35*).

It is noted that the optional language in the claim (i.e. "optional droplet" and "optional compartment") indicates that the feature does not have to be present in order to practice the claimed invention. Further, Blankenstein recites up to three liquids and Mehta discloses multiple compartments separated by bulkheads.

Blankenstein does not teach the magnet or conveyance means moving in a direction while applying a magnetic field, rather the magnet (8) is stationary as it's applying the magnetic field.

In the analogous art of particle separation in fluids, Ishiguro teaches a magnet that translate (*magnet 13, figure 3, [0011]*) that moves rightward in the fluidic apparatus that moves magnetic fluid that was introduced into microchannels (3) towards capacity portions (1, 2), for the benefit of driving magnetic particles across a distance within a channel.

It would have been obvious to one of ordinary skill in the art to use a moving magnet of Ishiguro in the apparatus of Blankenstein to drive magnetic particles across a distance within a channel.

**Regarding claim 24, Blankenstein teaches** a fluid out of said plural kinds to which said magnetic ultrafine particles are mixed and which is conveyed to said other small compartments (*the chamber of outlet 6 is where the magnetically stained particles are transferred, figure 1*) where fluid and said magnetic ultrafine particles are mixed and separated (*separation occurs after magnet 8 toward sort outlet 6, figure 1*).

Blankenstein does not teach by said conveyance means by passing through each bulkhead separating one small compartment from another to a droplet that includes said magnetic ultrafine particles and the droplet that does not include said magnetic ultrafine particles by using physical and chemical characteristics such as wettability and surface tension of said optional droplet.

However, Mehta teaches in column 16 line 55 - column 17 line 5, an array of flowable or fixed particles sets used in microfluidic systems where in a region of channel 210, several particle retention regions 220-250 (*the bulkheads are considered as the pillars that separate each retention region*). Particles sets 260-290, which can comprise magnetic beads (*column 3 line 4*) movable by a proximate magnet control applying a

magnetic field (*column 11 lines 1-5*) which are retained in the retention region, but communicated to neighboring regions by the narrow portion of channel 210, which fluid without the magnet particles flow through, (*See figure 2A*) for localizing the particles that have adhered to target cells or analytes and separating them from the fluid, thus providing methods for sequencing nucleic acids (*column 3 lines 3-35*).

Therefore, it would have been obvious to one of ordinary skill in the art at the time of the invention to add protrusion elements such as the bulkheads taught by Mehta in the fluidic system of Blankenstein to retain the magnetic beads or particles and separate them from the fluid, which can provide methods for sequencing nucleic acids (*column 3 lines 3-35*).

It is noted that the optional language in the claim (i.e. "optional droplet" and "optional compartment") indicates that the feature does not have to be present in order to practice the claimed invention. Further, Blankenstein recites up to three liquids and Mehta discloses multiple compartments separated by bulkheads.

**Regarding claim 25, Blankenstein teaches** controlling the magnetic field (*field by magnet 8*) which is externally applied to the fluid to which said magnetic ultrafine particles are mixed, said magnetic ultrafine particles are dispersed and cohered in the inside of the fluid, and also the operation of a specimen that adhered to surfaces of said magnetic ultrafine particles is performed. (*Column 3 line 65 – column 4 line 10 & column 5 line 60-65, column 6 line 20-35, & column 9 lines 10-40*).

**Regarding claim 26, Blankenstein** does not teach the physical and chemical reaction control by light, heat or pH is used.

However, Mehta teaches in (*column 5 lines 10-15*) teaches a control system that directs a plurality of mixings of the first reactant and the array wherein a reaction condition selected from temperature, pH, and time is systematically varied in separate mixings reactions. Other optional elements include a temperature control element for controlling temperature of reaction of the first and second element, a source of acid, a source of base and a source of reactants, reagents, array members, or the like (*column 5 lines 15-20*).

Therefore it would have been obvious to control the physical and chemical reaction conditions by heat, light, or pH, since the energy provided by these means are known to control the conditions of the reactions (*column 5 lines 15-20*).

**Regarding claim 27, Blankenstein** condition where a specimen for performing chemical reactive operation adhered (*magnetically stained particles, column 3 line 67 column 4 line 9*) to surfaces of said magnetic ultrafine particles, said magnetic ultrafine particles are used as a carrier to perform the chemical reactive operation to said specimen (*column 13 lines 1-15*).

**Regarding claims 28, Blankenstein does not teach** combining a plurality of said small compartments which are separated by plural bulkheads and which become said processing steps, at least a series of chemical reactive operation by reaction, separation and dilution to a specimen that adhered to surfaces of said magnetic ultrafine particles is performed.

However, Mehta teaches in (*column 16 line 55 - column 17 line 5*), an array of flowable or fixed particles sets used in microfluidic systems where in a region of channel 210, several particle retention regions 220-250 (the bulkheads are considered as the pillars that separate each retention region). Particles sets 260-290, which can comprise magnetic beads (*column 3 line 4*) movable by a proximate magnet control applying a magnetic field (*column 11 lines 1-5*) which are retained in the retention region, but communicated to neighboring regions by the narrow portion of channel 210, which fluid without the magnet particles flow through, (*See figure 2A*) for localizing the particles that have adhered to target cells or analytes and separating them from the fluid, thus providing methods for sequencing nucleic acids (*column 3 lines 3-35*).

Therefore, it would have been obvious to one of ordinary skill in the art at the time of the invention to add protrusion elements such as the bulkheads taught by Mehta in the fluidic system of Blankenstein to retain the magnetic beads or particles and separate them from the fluid, which can provide methods for sequencing nucleic acids (*column 3 lines 3-35*).

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***Response to Arguments***

Applicant's arguments with respect to claims 17-28 have been considered but are moot in view of the new ground(s) of rejection.

***Conclusion***

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Sharon Pregler whose telephone number is (571)270-5051. The examiner can normally be reached on Mon - Fri 8am-4pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, In Suk Bullock can be reached on (571)272-5954. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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Examiner, Art Unit 1772

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